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ATTORNEY DOCKET NO.: GENE1120-1

Applicants: Nolan and Filshie  
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**REMARKS**

Claims 1-29 were pending before this Response, with claims 3, 13-16, 18 and 23-29 being withdrawn from consideration due to a restriction requirement. By the present communication, claims 2-4, 6, 13-16, 18 and 23-29 have been cancelled without prejudice. In addition, claims 1, 5, 8 and 19-22 have been amended and new claims 30-39 have been added as shown in attached Exhibit A to define Applicants' invention with greater particularity. No new matter is introduced by the amendments, the new claim language being fully supported by the original specification and claims. Applicant submits that the claim amendments do not narrow the claims in any way within the meaning of Festo Corporation v. Shoketsu Kinzoku Kogyo Kabushiki Co. Ltd., a/k/a SMC Corporation and SMC Pneumatics, Inc. 234 F.3d 558, 51 U.S.P.Q. 2d 1959 (Fed. Cir. 2000). Accordingly, claims 1, 5-12, 19-22 and 30-39 are currently pending.

**The Restriction Requirement**

Applicants hereby confirm the election of Group I (claims 1-2, 4-12, 17, and 19-22) made without traverse during a telephone conversation with Applicants' representative, Lisa Haile, on September 24, 2001.

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### **The Drawings**

The Office Action asserts that the drawings on file are informal and requests submission of formal drawings upon allowance of the application. Applicants will submit formal drawings upon notification of allowance of claims pending in this application.

### **The Rejection under 35 U.S.C. §112, First Paragraph**

Applicants traverse the rejection of claims 1-2, 4-12, 17, and 19-22 under 35 U.S.C. § 112, First Paragraph, as allegedly lacking sufficient disclosure in the Specification to reasonably convey that the inventors had possession of the claimed invention at the filing of the application. Applicants disagree with the Examiner's assertion as basis of the rejection that the prior art provides "relatively few" embodiments of in vivo electroporation and that the Specification "provides almost no description" of in vivo embodiments of the claimed invention (Office Action, page 5-6).

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Applicants respectfully submit that the invention methods for introducing nucleic acid into a cell of a mammalian subject in vivo, as recited by amended claim 1 and new claim 39, are fully described in the Specification as supplemented by the knowledge of the art at the filing date of the application. The claims have been amended and new claims have been added to more particularly recite elements of the claimed invention, such as that nucleic acid is introduced into a cell of a mammalian subject in vivo, and that the invention utilizes a combination of "a low electrical field impulse of about 300 volts per centimeter to about 600 volts per centimeter and a long pulse length of about 10 milliseconds to about 100 milliseconds at or near the site of injection, wherein the impulse is of sufficient duration and strength to allow introduction of the nucleic acid into the cell." Such particularity addresses the Examiner's concern that the claims embrace a broad genus of potential combinations of nucleic acid composition, tissue-organism, electrode set-up, and electrical field-pulse duration-pulse frequency, such that one of skill on the art allegedly could not envision a representative number of specific embodiments of the claimed in vivo methods sufficient to describe the broadly claimed genus.

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In particular, Applicants disagree with the Examiner's assertion that the "prior art does not adequately compensate for the descriptive deficiencies of specification", and the conclusion based upon this assertion that those of skill in the art would conclude that applicants were not in possession of the claimed invention as of the priority date. The present application was filed June 28, 1999 as a continuation-in-part application claiming priority from USSN 09/103,477, filed June 24, 1998. Applicants have made of record in this application a number of references published as far back as 1991 that disclose methods of electrically-assisted *in vivo* delivery of genes using a variety of different procedures for delivering the nucleic acids (e.g., direct injection, intravenously, subcutaneously topically) to a variety of tissue sources (e.g., tumors, skin, vascular tissue) using a variety of electrode devices (e.g., flat steel electrodes, electrodes with reservoirs, catheter-electrode combinations, needle electrode arrays), and under a variety of electroporation conditions (none of which is the same as the claimed methods). In view of the amended scope of the present claims and the teachings in the art of record in this application, Applicants submit that the claimed genus is of such a scope that those of skill in the art would understand that the Applicants were in possession of the invention as of the priority date of this application. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, First Paragraph, for allegedly failing to describe the invention such that those of skill in the art would understand that the inventors had possession of the present scope of the claims at the priority date thereof.

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**The Rejection Under 35 U.S.C. § 112, Second Paragraph**

Applicants respectfully traverse the rejection of claims 1-2, 4-12, and 19-22 under 35 U.S.C. § 112, Second Paragraph, for allegedly being indefinite. With respect to the Examiner's assertion that the recitation of "a low electric field impulse" and a "long pulse length" renders claim 1 indefinite, claim 1 has been amended to provide specific ranges of electric field in terms of V/cm and a specific range of pulse length as measured in milliseconds.

With respect to the Examiner's assertion that the recitation of "a limited duration" renders claim 8 indefinite, claim 8 has been amended to delete both occurrences of the phrase "a limited duration", as pulse duration is recited in amended claim 1, thus rendering the rejection moot on this point.

With respect to the Examiner's assertion that the recitation of "the cells" in claims 19-22 is indefinite due to lack of proper antecedent basis in claim 1, claims 19-22 have been amended to delete "the cells" and now recite instead "the cell." Proper antecedent basis for "the cell" in claims 19-22 is now provided by the term "a cell" in line 1 of claim 1, rendering the rejection moot as to this point.

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In view of the above amendments and remarks, Applicants respectfully submit that presently pending claims 1, 5-12, 19-22 and 30-37 meet all requirements under 35 U.S.C. § 112, Second Paragraph, and reconsideration and withdrawal of the rejection are respectfully requested.

**The Rejection Under 35 U.S.C. § 102(e)**

Dev '710

Applicants respectfully traverse the rejection of claims 1-2, 4-11, 19-20 under 35 U.S.C. § 102(e) as allegedly being anticipated by Dev et al. (US 5,944,710; hereinafter "Dev '710"). Claims 2, 4, and 6 have been cancelled, thus the relevance of Dev '710 to claims 1, 5, 7-11, 17 and 19-20 and new claims 30-39 is addressed hereinbelow.

Applicants respectfully submit that the invention methods for introducing nucleic acid into a cell of a mammalian subject *in vivo*, as recited by amended claim 1 and new claim 37, distinguish over the disclosure of Dev '710 by reciting that the nucleic acid is introduced into a cell of a mammalian subject *in vivo* by a series of steps that comprises application of a low electric field impulse of about 300-600 V/cm for a long pulse length of about 10-100 milliseconds. Dev '710 is completely silent regarding use of such a *particular combination* of electric field impulse of about 300-600 V/cm and pulse length of about 10-100 milliseconds for introducing nucleic acid into a cell of a mammalian subject *in vivo*.

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Applicants disagree with the Examiner's assertion that disclosure in Dev '710 of intravascular delivery of nucleic acids using electroporation with electric fields of 100V/cm to several kV/cm; with a pulse length 100 microsecond to 100 millisecond anticipates the present claims. Dev '710 discloses a broad voltage range of at least 100-2,000V/cm (or higher), but Dev '710 teaches that "mammalian cells typically require between 0.5 and 5.0 kV/cm" before electroporation will occur (Dev, Col 10, lines 34-36). Thus, Dev '710 specifically discloses a field strength range appropriate for application of the invention claimed therein on mammalian cells begins at a voltage that excludes most of the voltage range recited in claims 1 and 39 of the present invention.

Moreover, there is no disclosure in Dev '710 that the combination of the above-discussed field strength and a pulse duration of 10-100 milliseconds is to be used for the case wherein nucleic acid is delivered to mammalian cells. Dev '710 discloses that the pulse length to be used for electroporation of cells can be between 100 microseconds to 100 milliseconds, preferably 500 microsecond to 10 millisecond. A pulse length of 0.76 milliseconds was used in the Example pointed to by the Examiner as allegedly anticipating the invention methods. Thus, Dev fails to disclose use of the particular combination of voltage range and pulse length recited in amended claims 1 and 39.

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Thus, Applicants respectfully submit that Dev '710 fails to disclose each and every element of claim 1 as would be necessary to establish anticipation under 35 U.S.C. § 102(e). Claims 5, 7-11, 17 and 19-20 and new claims 30-38 depend from Claim 1 and are not anticipated by Dev '710 for the same reasons as set forth for claims 1 and 39. Therefore, reconsideration and withdrawal of the rejection over Dev '710 are respectfully requested.

Dev '327

Applicants respectfully traverse the rejection of claims 1-2, 4-11, 19-20 under 35 U.S.C. § 102(e) as allegedly being anticipated by Dev et al. (US 5,859,327; hereinafter Dev '327). Claims 2, 4, and 6 have been cancelled, thus the relevance of Dev '327 to claims 1, 5, 7-11, and 19-20 and new claims 30-39 is addressed hereinbelow.

Applicants respectfully submit that the invention methods for introducing nucleic acid into a cell of a mammalian subject in vivo, as recited by amended claim 1 and new claim 39, distinguish over the disclosure of Dev '327 by reciting that the nucleic acid is introduced into a cell of a mammalian subject in vivo by a series of steps that comprises application of a low electric field impulse of about 300-600 V/cm for a long pulse length of about 10-100 milliseconds. Dev '327 is completely silent regarding use of such a particular combination of electric field impulse of about 300-600 V/cm and pulse length of about 10-100 milliseconds for introducing nucleic acid into a cell of a mammalian subject in vivo.

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By contrast, Dev '327 pertains to methods for delivery of nucleic acid to plant cells via electroporation. Because Dev '327 does not disclose any methods for introducing nucleic acid into a cell of a mammalian subject, Applicants respectfully submit that Dev '327 fails to anticipate claims 1, 5, 7-11, and 19-20 and new claims 30-39 under 35 U.S.C. § 102(e). Claims 5, 7-11, and 19-20 and new claims 30-38 depend from Claim 1 and are not anticipated by Dev '327 for the same reasons as set forth for claims 1 and 39. Therefore, reconsideration and withdrawal of the rejection over Dev '327 are respectfully requested.

**The Rejection Under 35 U.S.C. § 102(a)**

**Yamazuki**

Applicants respectfully traverse the rejection of claims 1-2, 4-12, and 19-20 under 35 U.S.C. § 102(a) as allegedly being anticipated by Yamazaki et al. (Biol. Repro. Dec. 1998; hereinafter "Yamazaki").

Without commenting on the merits of the Examiner's allegations, Applicants assert that Yamazaki was published after the priority date of the present application and, thus, is not available as a reference under 102(a). The present application was filed June 28, 1999, as a CIP claiming priority from USSN 09/103,477, filed June 24, 1998. Accordingly, Applicants respectfully submit that the rejection over Yamazaki is moot and reconsideration and withdrawal of the rejection are respectfully requested.

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In view of the above amendments and remarks, reconsideration and favorable action on claims 1, 5, 7-12, 17, 19-22 and 30-39 are respectfully requested. If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' representative, Lisa A. Haile, J.D., Ph.D., can be reached at (858) 677-1456.

Respectfully submitted,

Date: April 2, 2002

*June M. Learn*  
June M. Learn  
Registration No.: 31, 238  
Telephone: (858) 677-1416  
Facsimile: (858) 677-1465

**USPTO CUSTOMER NUMBER 28213**  
GRAY CARY WARE & FREIDENRICH LLP  
4365 Executive Drive, Suite 1100  
San Diego, California 92121-2133

Enclosure: Exhibit A

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**EXHIBIT A**

**Version with Markings to Show Changes Made**

Please amend claims 1, 5, 8, and 19-22 as follows:

1. (Amended) A method for introducing nucleic acid into a cell of a mammalian subject in vivo, comprising:

contacting the [cell] mammalian subject with [a] an isolated nucleic acid sequence via injection of the nucleic acid into the subject at a site near the cell into which the nucleic acid is to be introduced; and

applying a low electrical field impulse of about 300 volts per centimeter to about 600 volts per centimeter for a long pulse length of about 10 milliseconds to about 100 milliseconds at or near the site of injection, wherein the impulse is of sufficient duration and strength to [introduce] allow introduction of the nucleic acid into the cell.

5. (Amended) The method of claim [4] 1, wherein the low electrical field impulse is from about 400-500 volts per centimeter.

8. (Amended) The method of claim 1, wherein the electrical impulse is selected from the group consisting of a square wave pulse, an exponential wave pulse, a unipolar oscillating wave form [of limited duration], and a bipolar oscillating wave form [of limited duration].

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19. (Amended) The method of claim 1, wherein the [cells are] cell is a nondividing [cells] cell.

20. (Amended) The method of claim 1, wherein the [cells are] cell is a dividing [cells] cell.

21. (Amended) The method of claim 1, wherein the [cells are] cell is a hematopoietic [cells] cell.

22. (Amended) The method of claim 21, wherein the [cells are] cell is a stromal [cells] cell.

Please add the following new claims 30-39:

-- 30. (New) A method of claim 1, wherein the cell is a muscle cell.

31. (New) A method of claim 1, wherein the cell is a vascular cell.

32. (New) A method of claim 1, wherein the cell is a skin cell.

33. (New) A method of claim 1, wherein the cell is a tumor cell.

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34. (New) A method of claim 1, wherein the nucleic acid modulates the expression of a gene in the cell.

35. (New) A method of claim 1, wherein the nucleic acid encodes an immunomodulatory agent.

36. (New) A method of claim 1, wherein the nucleic acid encodes a therapeutic protein.

37. (New) A method of claim 1, wherein the nucleic acid encodes a biological response modifier.

38. (New) A method of claim 1, wherein the nucleic acid encodes an antibody molecule.

39. (New) A method for introducing nucleic acid into a cell of a mammalian subject in vivo, comprising:

contacting the mammalian subject in vivo with an isolated nucleic acid sequence via perfusion of the nucleic acid into the subject; and  
applying a low electrical field impulse of about 300 volts per centimeter to about 600 volts per centimeter for a long pulse length of about 10 milliseconds to about 100 milliseconds at or near the cell into which the nucleic acid is to be introduced, wherein the impulse is of sufficient duration and strength to allow introduction of the nucleic acid into the cell. --